1 438 819

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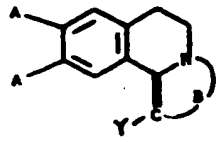
(54) IMPROVEMENTS IN FUSED-RING ISOQUINOLINE DERIVATIVES

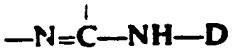
(71) We, CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT., a Hungarian Body Corporate, of 1—5 To-utca, Budapest IV, Hungary, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns fused-ring isoquinoline derivatives and more particularly is directed to new imidazo[5,1-a], and pyrazolo[5,1-a]-isoquinolines of the general formula I, and acid addition salts thereof:—



(I)

wherein
A represents an alkoxy group containing 1—4 carbon atoms,
B represents a

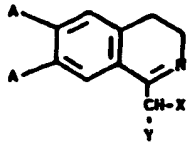


group, wherein D is hydrogen, alkyl, aralkyl, cycloalkyl or acyl,
Y represents hydrogen, cyano, carbamoyl, alkoxycarbonyl, alkyl, or aralkyl or phenyl each optionally substituted by one or more substituents selected from halogen atoms, alkoxy and nitro groups.

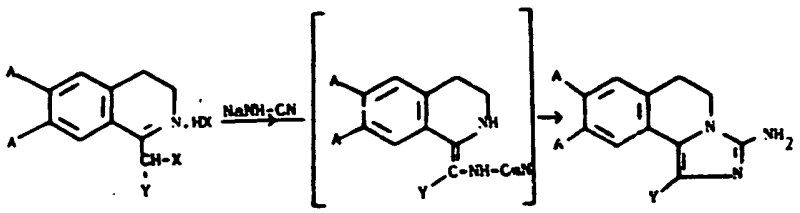
We have found that compounds of the general formula I which we have tested decrease the resistance to coronary perfusion, increase the perfusion, moderate the oxygen consumption of the heart muscle, improve the ratio of O_2 supply/O_2 demand expressing the oxygenation of the heart, and influence in an advantageous way the efficiency of the heart-labour.

Methods we have devised for the preparation of the compounds of formula I form other aspects of our invention.

According to one such method aminoimidazole derivatives of the general formula I wherein A is as defined above, D is hydr gen and Y is as defined above, may be prepared by reacting corresponding isoquinoline derivatives of the general formula II



wherein X is halogen, with an alkali metal salt or alkaline earth metal salt of cyanamide, e.g. with sodium hydrogen cyanamide. We believe that an intermediate N-monosubstituted cyanamide is obtained which cyclizes with the nitrogen of the iso-basic isoquinoline to form a cyclic guanidine, namely a compound of the general formula Ia as illustrated below:—

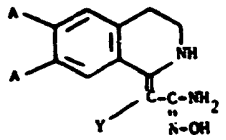


II Ia

The reaction may be carried out with a compound of the general formula II wherein the methylene group attached to the halogen is unsubstituted or is already substituted with Y, wherein Y is preferably cyano, phenyl or substituted phenyl.

The compounds of the general formula II may be prepared by cyclizing the acylated derivative of the corresponding 2-phenyl-ethylamine, e.g. a derivative acylated with a carboxylic acid halide, by the Bischler-Napieralski reaction.

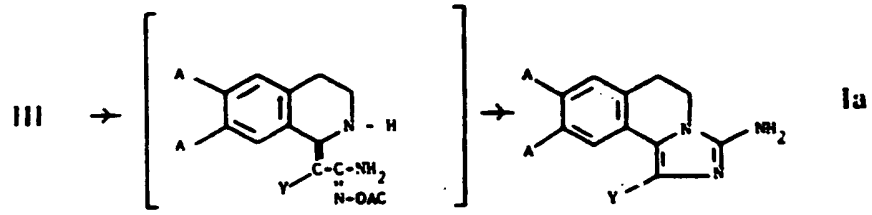
Compounds of the general formula I wherein D represents hydrogen or acyl and Y represents hydrogen, alkyl, or aralkyl or phenyl each optionally substituted as defined above may be prepared by acylating isoquinolyl-acetamidoxime of the general formula



III

wherein Y is as defined above and allowing the O-acyl intermediate thus produced to be transformed to an imidazo[5,1-a]-isoquinoline derivative under basic conditions. The acylation may be performed with a sulphonyl halide, especially a sulphonyl chloride, or with a carboxylic acid derivative.

It is known that by acylating amidoximes O-acyl-derivatives are obtained [Chem. Reviews, 62 155 (1962)]. Some of these O-acyl-derivatives e.g. the tosylates are capable of liberating acid and hypothetically forming N-substituted cyanamides by Beckmann rearrangement, which then cyclise to isoquinoline derivatives:—



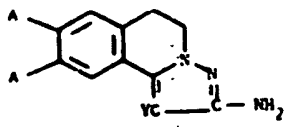
III Ia

According to a particularly advantageous embodiment of this process the acylation is carried out in a basic medium e.g. pyridine and as acylating agent a sulfonyl chloride, carboxylic acid chloride or carboxylic acid anhydride is used.

The preparation of the compounds of the general formula III is described in Hungarian Patent Specificati n No. 156,811.

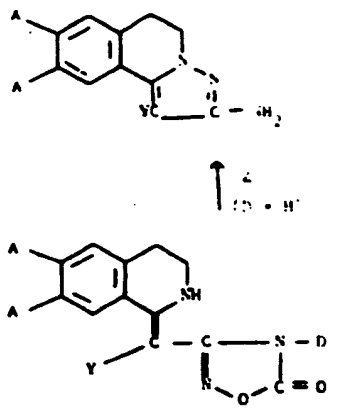
Aminoimidazoles of the general formula Ia wherein D represents an acyl group may be prepared by using the acylating agent in excess, whereby the exocyclic amino group is acylated too (NH—Ac).

The amino-pyrazole derivative of the general formula Ib



Ib

may be prepared by heating of a corresponding oxadiazol-5-one of the general formula IV:



IV

It is known, that carbon dioxide may be eliminated from oxadiazole-5-one compounds [J. Heterocyclic Chem. 7 59 (1970)], but the obtained product is very seldom homogeneous [Chem. Ber. *105* 813 (1972)].

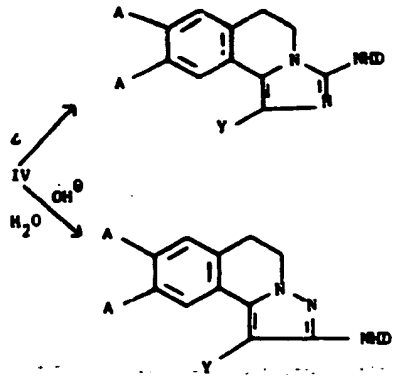
According to the present invention the reaction described above may be carried out by heating in a melt or in an apolar solvent, particularly in xylene or tetralin with a good yield. The reaction has been carried out at a temperature above 100°C. The same products may be prepared by the alkaline hydrolysis (e.g. alkali metal hydroxide) of the compounds of the general formula IV (D=H) e.g. at the boiling point. These reactions are primarily applicable to compounds wherein Y is hydrogen, cyano, carbamoyl, alkyl, or aralkyl or phenyl each optionally substituted as defined above.

Compounds of the general formula IV may be prepared by cyclizing the corresponding N-(2-phenethyl)-1,2,4-oxadiazoline-5,3-yl acetamide derivatives by the Bischler-Napieralski reaction.

Compounds of the general formula Ia and Ib substituted in the exocyclic amino group are prepared in the following way:

a) compounds of the formula Ia and Ib containing an unsubstituted amino group, previously prepared, may be converted e.g. by acylation, or by reductive alkylation (when Y is other than alkoxycarbonyl) with an aldehyde or ketone through a derivative of azomethine, or

b) a 1,2,4-oxadiazole-5-one derivative of the general formula IV already substituted on N^4 may be subjected to alkaline hydrolysis or heated above 100°C in a solvent or in melt form. The first method yields pyrazolo-, the second imidazo-derivatives:—



Ia

Ib

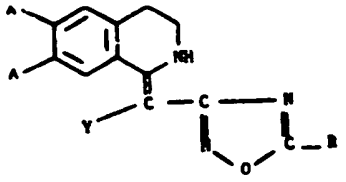
wherein

D is alkyl, cycloalkyl or aralkyl. The reactions are applicable to compounds wherein Y has the aforementioned values.

When a compound of the general formula Ia or Ib of known structure which is unsubstituted is afterwards substituted on the exocyclic nitrogen with the group D e.g. by reductive condensation, a definite distinction can be made between the imidazo and pyrazolo derivatives. Products so obtained may then be compared with the product obtained from an N^4-substituted-1,2,4-oxadiaz le-5-one of the general formula IV, and thus the product may be identified.

In other cases it may be decided by proton-resonance spectroscopy if a compound belongs to the Ia or Ib comp und group. If both condensed five-membered rings contain ne C—H bond, this bond is attached to N in the structure Ia and to C in the structure Ib and thus the chemical shift of the methine proton is characteristic for the structure.

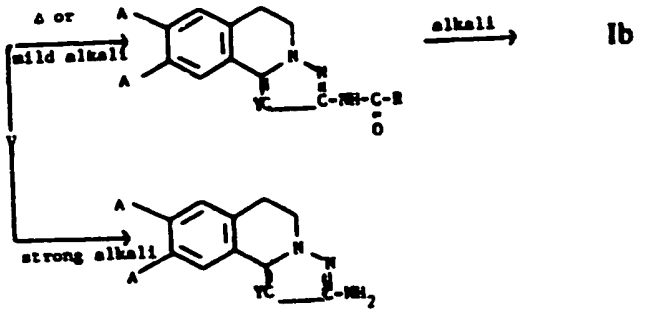
Aminopyrazoles of the general formula Ib and N-acyl derivatives thereof may be also prepared from the compounds of the general formula V



V

wherein
R is alkyl, aryl or aralkyl optionally substituted with nitro, halogen or alkoxy,
Y is hydrogen, alkyl or aralkyl or phenyl each optionally substituted by one or more substituents selected from halogen atoms, alkoxy and nitro groups.

N-acyl derivatives are formed under mildly alkaline conditions or on heating in melt or in a solvent, or compounds of the general formula Ib (wherein D stands for hydrogen) are directly formed on strong alkaline hydrolysis.



Ib

Ib

Compounds of the general formula I may be subsequently converted at the methine group of the five membered condensed ring, by methods known *per se*. Said process may be carried out with compounds of the general formula I wherein D is an acyl-protecting group and if desired after the introduction of Y the protecting group may be removed by hydrolysis. By reduction of the azo-compounds according to a known method, compounds may be formed wherein $Y=NH_2$.

Compounds of the general formula I — wherein Y is cyano — may be hydrolyzed or alcoholized to form compounds of the general formula I wherein Y is carbamoyl or alkoxycarbonyl. Compounds wherein D is acyl may be hydrolysed to those in which D is hydrogen.

Acid addition salts of the compounds of the general formula I may be also prepared by reacting the compounds of the formula I with mineral or organic acids or conversely the corresponding base may be set free from an acid addition salt thereof.

The pharmacological tests described below were carried out on anaesthesized dogs [Nembutal (registered Trade Mark) 25 mg/kg i.v. according to the following methods:

1. *Effect on the arterial pressure*. The arterial medium pressure was measured directly in the carotid artery of the dogs, by the insertion of a Statham measuring instrument with Hellige (registered Trade Mark) electromanometer and was registered by a Hellige multiscriptor continuously. The results are illustrated in table 1.

2. *Coronary dilating effect*. The coronary perfusion was measured by a thermodilutional process based on constant, steady cold liquid-infusion into the sinus coronarius [Szekeres L., Papp J.Gy., Fischer, E.: Acta Physiol. Acad. Sci. Hung. *33*, 115 (1969)] and was registered with the aid f a thermoelement, introduced also into the sinus cor narius, on a KIPP Micrograph c ntinuously and

was expressed in a voluntary unit, as a ratio of the arterial medium pressure (Hgmm.) and of the coronary perfusion, measured in the sinus coronarius (ml/min/100 g.). The results are summerized in the table II.

3. *Effect on the oxygenization of the heart.* In the course of the test carried out on dogs simultaneously with the measuring of the coronary perfusion the oxygen saturation of the blood sample, sucked with steady speed with peristaltic pump through the KIPP Oxymeter from the sinus coronarius and let back to the branchial vein, was continuously registered. The oxygen saturation of the arterial blood and the haemoglobin content of the blood was also determined with the aid of a Zeiss haemometer. Knowing these data the oxygen consumption of the left heart ventricle was calculated (ml/100 g./min.). To characterize the oxidative metabolism of the heart muscle and of the sufficiency of the oxygen the O_2 supply/O_2 demand ratio was also calculated. Details can be found in Szekeres, L., Papp, J.Gy., Fischer, E.: European J. Pharmacol. 2, 1 (1967). The results are shown in the table III.

4. *Effect on the efficiency of the labour of the left heart ventricle.* The extent of the effect on the efficiency of the labour of the left heart ventricle was determined on the basis of the labour of the left heart ventricle, calculated from the cardiac output, registered according to the method cold liquid-infusion (Szekeres, L., Papp, J. Gy., Fischer, E.: Acta Physiol. Acad. Sci. Hung., *33*, 115 (1969)) and from the arterial medium pressure, also knowing the oxygen consumption of the left ventricle, calculated as described above on the basis of the ratio of the labour of the left heart ventricle (mkg./min.): and of the oxygen consumption of the left heart ventricle (ml./min./100 g.). The results are shown in the table IV.

5. *Toxicity.* The acute toxicity investigations were carried out on rats of a bodyweight 150—200 g. The dose was injected in the caudal vein, within maximum 5 seconds in a volume of 0.2 ml./100 g. The LD_{50} value and the tolerance limits were determined on the basis of the number of the animals dead within 24 hours, according to the method of Litchfield and Wilcoxon (J. Pharmacol. exp. Ther., 96, 99 (1949)).

For pharmaceutical use, the compounds of the present invention may be formulated as pharmaceutical compositions containing as active ingredient a compound of the formula I or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutically acceptable organic or inorganic carrier or diluent.

The products may be in the form of e.g. tablets, capsules or suppositories; or in liquid form, e.g. as a solution, emulsion or suspension. The products may contain auxiliary materials as stabilizers, wetting, emulsifying and suspending agents or salts or buffers causing the alteration of the osmotic pressure and further pharmaceutically acceptable excipients, and/or further pharmaceutically active substances.

Further details of the present invention are illustrated in the following non-limitative examples.

Example 1a.

6.0 g. of technical calcium cyanamide are suspended with heating in 15 ml. of water and 8.0 ml. of 10% sodium hydroxide are added. The mixture is heated for 15 minutes at 50—60°C and the precipitate is filtered off.

150 ml. of alcohol are added to the filtrate and the mixture is boiled under reflux.

2.7 g. of 1-chloromethyl-6,7-dimethoxy-3,4-dihydro-isoquinoline-hydrochloride are added to the boiling solution within half an hour. Subsequently the reaction mixture is boiled for 4 hours and evaporated to dryness *in vacuo*. 50 ml. of water are added to the residue and the crystalline substance is filtered by suction and dried. 1.8 g. of 3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are obtained. m.p.: 232—236°C. The product is purified by recrystallization from alcohol.

Analysis: $C_{13}H_{15}N_3O_2$

	Calculated	Found
C:	63.65%	63.42%
H:	6.16%	6.32%
N:	17.13%	16.92%

The proton in the 1-position appears at 6.70 ppm. in $CDCl_3$—DMSO solution in the NMR spectrum of the product.

Example 1b.

13.2 g. of [6,7-dimethoxy-3,4-dihydro-2H-isoquinolylidene-(1)]-acetamidoxime and 50 ml. of pyridine are mixed together, and while stirring and cooling 9.6 g. of tosyl chloride are added within 15 minutes. The reaction mixture is subsequently stirred for 2 hours at 70°C and allowed to stand for one night in the refrigerator. The precipitated product is filtered by suction, washed with absolute alcohol and dried. 9.2 g. of 3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]-isoquinoline-hydrochloride are obtained. M.p.: 272—274°C (from alcohol). The hydrochloride salt is dissolved in hot water and to set free the base, the solution is basified with 10% sodium hydroxide solution. A crystalline base is obtained, which is identical to the product of the example 1a.

Example 1c.

According to the method described in the Example 1b 25.6 g. of 3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline-hydrochloride are obtained from 29.0 g. of [6,7-dimethoxy-3,4-dihydro-2H-isoquinolyidene-(1)]-acetamidoxime and from 13 ml. of benzoyl chloride; the product is identical to that of the product of the Example 1b.

The same product is obtained if in the above reaction ethyl chlorocarbonate is used instead of benzoyl chloride.

Example 2.

14.56 g. of [6,7-diethoxy-3,4-dihydro-2H-isoquinolylidene-(1)]-acetamidoxime and 60 ml. of pyridine are mixed and while stirring and cooling 7.6 g. of benzoyl chloride are added. Subsequently the mixture is stirred at 50—60°C, and the solvent is evaporated *in vacuo*. The residue is suspended in ethyl acetate and thus 12.65 g. of 3-amino-5,6-dihydro-8,9-diethoxy-imidazo[5,1-a]isoquinoline-hydrochloride-monohydrate are obtained. Mp.: 206—208°C (from alcohol).

Analysis: $C_{15}H_{22}N_3O_2Cl$

	Calculated:	Found:
C:	54.96%	54.81%
H:	6.77%	6.64%
N:	12.81%	12.76%
Cl:	10.82%	10.69%

The said hydrochloride salt is dissolved in 70 ml. of warm water, the solution is clarified with charcoal, filtered and basified with 10% sodium hydroxide solution. 9.7 g. of 3-amino-5,6-dihydro-8,9-diethoxy-imidazo[5,1-a]isoquinoline are obtained. Mp.: 212—217°C (from alcohol).

Analysis: $C_{15}H_{19}N_3O_2$

	Calculated:	Found:
C:	65.91%	66.10%
H:	7.01%	6.95%
N:	15.37%	15.22%

Example 3.

3.2 g. of technical calcium cyanamide are mixed in 9 ml. of 10% sodium hydroxide for a quarter of an hour at 60—70°C and the mixture is filtered. 80 ml. of alcohol are added to the filtrate, the mixture is boiled and 3.34 g. of 1-(1-chloroethyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline-hydrochloride are added to the boiling mixture [Arch. der Pharm. *277*, 177, (1939)]. The reaction mixture is evaporated after boiling for 5 hours and water is added to the residue. 2.0 g. of 1-methyl-3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are obtained. Mp.: 248—250°C (from absolute alcohol).

Analysis: $C_{14}H_{17}N_3O_2$

	Calculated:	Found:
C:	64.84%	65.08%
H:	6.61%	6.63%
N:	16.21%	16.44%

Example 4.

200 mg. of 3-[6,7-dimeth xy-3,4-dihydro-2H-1-isoquinolyidene]-methyl-5-

benzyl-1,2,4-oxadiazole are added to 5 ml. of xylene and the reaction mixture is boiled for 8 hours, under reflux. After cooling 10 ml. of petrol ether are added to the mixture. 170 mg. of 2-phenylacetylamino-5,6-dihydro-8,9-dimethoxy-pyrazolo-[5,1-a]isoquinoline are obtained. Mp.: 225—227°C (from butanol).

Analysis: $C_{21}H_{21}N_3O_3$

	Calculated:	Found:
C:	69.40%	69.50%
H:	5.82%	5.80%
N:	11.56%	11.45%

Example 5a.

5 g. of 3-[6,7-dimethoxy-3,4-dihydro-2H-1-isoquinolylidene]-methyl-Δ^2-1,2,4-oxadiazolin-5-one are melted on a hot plate at 180—200°C. After cooling the solid product is dissolved under heating in 30 ml. of 5% aqueous hydrochloric acid, the solution is filtered and basified with 10% sodium hydroxide. The crystallized product is filtered, washed with water and dried. Thus 3 g. of 2-amino-5,6-dihydro-8,9-dimethoxypyrazolo[5,1-a]isoquinoline are obtained. Mp.: 216—217°C (from alcohol).

Analysis: $C_{13}H_{15}N_3O_2$

	Calculated:	Found:
C:	63.65%	63.45%
H:	6.16%	6.40%
N:	17.13%	16.95%

The proton in the 1-position appears at 5.85 ppm. in the NMR spectrum of the product.

Example 5b.

65 ml. of xylene are added to 13 g. of 3-[6,7-dimethoxy-3,4-dihydro-2H-1-isoquinolylidene]-methyl-Δ^2-1,2,4-oxadiazolin-5-one and the reaction mixture is boiled under reflux for 3 hours. After cooling the precipitated crystals are filtered and dried. Thus 10 g. of 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline are obtained. The product is identical to the product described in Example 5a.

By treatment with alcoholic HCl of a solution of the product in 96% alcohol, the hydrochloride salt, 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline-hydrochloride-dinydrate is crystallized. Mp.: 128—130°C.

Analysis: $C_{13}H_{20}N_3O_4Cl$

	Calculated:	Found:
C:	49.13%	49.30%
H:	6.34%	6.11%
N:	13.22%	12.98%
Cl:	11.16%	11.27%

Example 5c.

20 ml. of 10% sodium hydroxide are added to 1.6 g. of 3-[6,7-dimethoxy-3,4-dihydro-2H-1-isoquinolylidene]-methyl-Δ^2-1,2,4-oxadiazolin-5-one and the reaction mixture is boiled under reflux for 8 hours. After cooling 0.9 g. of 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline is crystallized and the product is identical to the product described in the Example 5a. The LD_{50} value and the 95% tolerance limits are 70 (34—148) mg/kg.

As stated above the product decreases the arterial blood pressure in a dose of 1—4 mg-kg i.v., increases the coronary perfusion, decreases the coronary resistance, decreases the oxygen consumption of the heart muscle and improves i.e. increases the ratio O_2 supply/O_2 demand expressing the oxygenation of the heart and thus influences favourably the efficiency of the heart labour. All these facts show, so far as we can judge from animal tests, the compound meets the requirements of antianginal agents.

TABLE I

Dose (mg/kg i.v.)	n	Arterial blood pressure		
		Basic value (Hgmm.)	Altered value (Hgmm.)	Difference (%)
1	5	127	104	- 18
2	5	124	92	- 26
4	6	105	67	- 36

TABLE II

Dose (mg/kg i.v.)	n	Coronary perfusion ml./min./100 g.			Coronary resistance (Hgmm./ml./min/100 g)		
		Basic value	Altered value	Diff. (%)	Basic value	Altered value	Diff. (%)
1	5	24	87	+ 4	1.86	1.46	- 22
2	5	82	100	+ 22	1.90	1.31	- 31
4	6	84	108	+ 29	1.33	0.71	- 47

TABLE III

Dose (mg/kg. i.v.)	n	O_2 consumption of left heart ventricle (ml./min./100 g.)			O_2 supply/O_2 consumpt. of left heart ventr.		
		Basic value	Altered value	Diff. (%)	Basic value	Altered value	Diff. (%)
1	5	9.8	8.0	- 18	1.48	1.68	+ 14
2	5	9.4	7.5	- 20	1.51	1.93	+ 28
4	6	8.7	8.7	–	1.77	2.12	+ 20

TABLE IV

Dose (mg/kg i.v.)	n	Efficiency of labour of left heart ventr.		
		Basic value	Altered value	Difference (%)
1	5	0.35	0.49	+40
2	5	0.36	0.46	+28
4	6	0.27	0.35	+22

Example 6a.

50 ml of alcohol and 10 ml. of 10% sodium hydroxide are added to 1.75 g. of 3-[6,7-dimethoxy-3,4-dihydro-2H-1-isoquinolylidene]-methyl-5-phenyl-1,2,4-oxadiazole and the reaction mixture is boiled under reflux for 3 hours. The alcohol is evaporated *in vacuo* and water is added to the residue. Thus 1.2 g. of 2-benzoyl amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline are obtained, the product is identical to the product described in Example 17.

Example 6b.

10 ml. of xylene are added to 1 g. of 3-[6,7-dimethoxy-3,4-dihydro-2H-1-iso-

quinolylidene]-methyl-5-phenyl-1,2,4-oxadiazole and the reaction mixture is boiled under reflux for 8 hours. After cooling 0.9 g. of 2-benzoyl-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline crystallizes, the product is identical with the product of the Example 6a.

Example 7.

25 ml. of alcohol and 7 ml. of 40% sodium hydroxide are added to 1 g. of 3-[6,7 - dimethoxy-3,4-dihydro-2H-1-isoquinolylidene]-methyl-5-phenyl-1,2,4-oxadiazole and the reaction mixture is boiled under reflux for 8 hours. Subsequently the alcohol is evaporated *in vacuo* and water is added to the residue. 0.6 g. of 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline are crystallized and the product is identical to the product described in Example 5.

Example 8a.

2 g. of 3-(6,7-dimethoxy-3,4-dihydro-2H-1-isoquinolylidene)-methyl-4-benzyl-Δ^2-1,2,4-oxadiazolin-5-one are melted on a hot plate at 170—180°C. After cooling the product is crystallized from benzene and thus 1.2 g. of 3-benzyl-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are obtained. Mp.: 135°C.

Analysis: $C_{20}H_{21}N_3O_2$

	Calculated:	Found:
C:	71.62%	71.52%
H:	6.31%	5.98%
N:	12.53%	12.42%

The proton in the 1 position appears at 6.85 ppm. in the NMR spectrum of the product.

Example 8b.

10 ml. of xylene are added to 1.5 g. of 3-(6,7-dimethoxy-3,4-dihydro-2H-1-isoquinolylidene)-methyl-4-benzyl-Δ^2-1,2,4-oxadiazolin-5-one and the mixture is boiled under reflux for 2 hours. After cooling, 1.1 g. of 3-benzylamino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are crystallized, the product is identical to that described in Example 8a.

Example 8c.

1.1 g. of benzaldehyde and 20 ml. of absolute alcohol are added to 2.3 g. of 3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline and the reaction mixture is boiled under reflux for 5 hours. After cooling 3.1 g. of 3-benzylidene-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are crystallized. Mp.: 176°C (from alcohol).

Analysis: $C_{20}H_{19}N_3O_2$

	Calculated.	Found:
C:	72.05%	72.35%
H:	5.75%	5.80%
N:	12.61%	12.69%

1.6 g. of the said product are dissolved in 100 ml. of methanol and 0.5 g. of sodium borohydride are added to the solution within half an hour. Subsequently the solution is allowed to stand at room temperature whereafter the solvent is evaporated. Water is added to the residue, which crystallizes. The product is filtered and dried. 1.7 g. of 3-benzylamino-5,6-dihydro-8,9-dimethoxy-imidazo-[5,1-a]isoquinoline are obtained and the product is identical to that of Example 8a.

1.7 g. of the above product are dissolved in hot methanol and the warm solution is acidified with methanolic HCl. After cooling, 1.4 g. of 3-benzylamino-5,6 - dihydro - 8,9 - dimethoxy - imidazo[5,1-a]isoquinoline - hydrochloride are crystallized. Mp.: 250—252°C.

Analysis: $C_{20}H_{22}N_3O_2Cl$

	Calculated:	Found:
C:	64.59%	64.48%
H:	5.96%	6.02%
N:	11.31%	11.50%
Cl:	9.53%	9.31%

The compound increases the contractility by 40% in a dose of 1—2 mg/kg. for 26—28 minutes. The cardiac output is increased by 30% in narcotized dogs in a dose of 2 mg./kg., the duration of the effect is 16 minutes. The resistance of the pulmonary vascular system is decreased in a dose of 2 mg./kg. for 22 minutes. The compound improves the efficiency of the heart function of the narcotized dog. In a dose of 0.5 mg./kg. the compound causes a 77% increase of the femoral perfusion in narcotized dogs for 16 minutes. It increases the perfusion of the carotid system by 31% for 24 minutes in a dose of 1 mg./kg. The compound increased the electric fibrillar threshold of the *in situ* cat heart atrial muscle system by 104% in a dose of 2 mg./kg. The compound increased the electric fibrillar threshold of the *in situ* cat heart ventricle muscle-system in a dose of 2 mg./kg. by 50% for 41 minutes and by 82% in a dose of 4 mg./kg.

Example 9a.

70 ml. of 10% sodium hydroxide and 400 ml. of alcohol are added to 10 g. of 3-(6,7-dimethoxy-3,4-dihydro-2H-1-isoquinolylidene)-methyl-4-benzyl-Δ^2-1,2,4-oxadiazolin-5-one and the reaction mixture is boiled under reflux for an hour. Subsequently the mixture is evaporated to dry *in vacuo* and water is added to the residue. 8 g. of 2-benzylamino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline are obtained. Mp.: 156°C (from alcohol).

Analysis: $C_{20}H_{21}N_3O_2$

	Calculated:	Found:
C:	71.62%	71.86%
H:	6.31%	6.08%
N:	12.53%	12.64%

Example 9b.

0.6 g. of benzaldehyde and 10 ml. of absolute alcohol are added to 1.2 g. of 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline and the reaction mixture is boiled under reflux for hours. After cooling 1.1 g. of 2-benzylidene-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline are obtained in crystalline form. Mp.: 163°C.

Analysis: $C_{20}H_{19}N_3O_2$

	Calculated:	Found:
C:	72.05%	71.88%
H:	5.75%	6.01%
N:	12.61%	12.50%

0.9 g. of the above product are dissolved in 100 ml. of methanol and 0.2 g. of sodium borohydride are added to the solution. The solution is allowed to stand for an hour whereafter the solvent is evaporated *in vacuo*. Water is added to the residue. Thus 0.8 g. of 2-benzyl-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]-isoquinoline are obtained, the product is identical to that of Example 9a.

5.7 g. of the above product are dissolved in 80 ml. of acetone and the solution is acidified with absolute alcoholic HCl.

5.5 g. of 2-benzylamino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline-hydrochloride are crystallized. Mp.: 206—208°C.

Analysis: $C_{20}H_{22}N_3O_2Cl$

	Calculated:	Found:
C:	64.59%	64.70%
H:	5.96%	6.12%
N:	11.31%	11.52%
Cl:	9.53%	9.38%

The proton in the 1-position appears at 5.73 ppm. in the NMR spectrum of the product.

Example 10.

14 ml. of 10% sodium hydroxide and 80 ml. of alcohol are added to 2 g. of 3-(6,7-diethoxy-3,4-dihydro-2H-1-isoquinolylidene)-methyl-4-benzyl-Δ^2-1,2,4-oxadiazolin-5-one and the reaction mixture is boiled under reflux for an hour. Subsequently the mixture is evaporated to dry and water is added to the residue.

Thus 1.5 g. of 2-benzylamino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline are obtained. Mp.: 130—131°C (from butanol).

Analysis: $C_{22}H_{23}N_3O_2$

	Calculated:	Found:
C:	72.70%	72.51%
H:	6.93%	6.86%
N:	11.56%	11.80%

Example 11.

5 ml. of acetic anhydride are added to 1 g. of 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline, the reaction mixture is heated on water bath for 10 minutes and allowed to stand for an hour. After pouring on ice 0.8 g. of 2-acetylamino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline are crystallized. Mp.: 223°C (from 75% alcohol).

Analysis: $C_{15}H_{17}N_3O_3$

	Calculated:	Found:
C:	62.70%	62.56%
H:	5.96%	5.78%
N:	14.63%	14.60%

Example 12.

20 ml. of chloroform and 1.4 g. of potassium carbonate are added to 2.45 g. of 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline and 1.15 g. of chloroacetyl chloride are added under stirring. Subsequently the mixture is stirred for 5 hours at room temperature and 20 ml. of water are added. The chloroform phase is separated, dried over sodium sulphate and evaporated. 2 g. of 2-chloro-acetyl-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline are obtained. Mp.: 152—154°C (from alcohol).

Analysis: $C_{17}H_{18}N_3O_3Cl$

	Calculated:	Found:
C:	55.99%	56.10%
H:	5.01%	4.93%
N:	13.06%	12.80%
Cl:	11.02%	10.82%

Example 13.

30 ml. of acetic anhydride are added to 8 g. of 3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline and the mixture is heated on a water bath for half an hour. The mixture is poured on 150 ml. of ice water. The solution is neutralized with sodium carbonate and the precipitated crystals are filtered. Thus 6.2 g. of 3-acetyl-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are obtained. Mp.: 225°C (from absolute alcohol).

Analysis: $C_{15}H_{17}N_3O_3$

	Calculated:	Found:
C:	62.70%	62.40%
H:	5.96%	5.90%
N:	14.63%	14.69%

Example 14.

30 ml. of chloroform and 1.4 g. of potassium carbonate are added to 2.45 g. of 3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline and under stirring 1.15 g. of chloroacetyl chloride are added. The mixture is stirred at room temperature for 5 hours and 20 ml. of water are added. The chloroform solution is separated, dried over sodium sulphate and evaporated. 1.4 g. of 3-chloro-acetyl-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are obtained. Mp.: 251°C (from alcohol).

Analysis: $C_{17}H_{18}N_3O_3Cl$

	Calculated:	Found:
C:	55.99%	56.20%
H:	5.01%	4.93%
N:	13.06%	12.84%
Cl:	11.02%	11.16%

Example 15.

1 g. of technical calcium cyanamide are suspended in 5 ml. f lukewarm water and 1.4 ml. of 10% sodium hydroxide are added. The mixture is stirred at 50 to 60° for a quarter of an hour and the precipitate is filtered. 50 ml. of alc hol are added to the filtrate and the mixture is boiled. 1 g. of α-brom -6,7-dimethoxy-3,4-dihydro-1-isoquinolyl acetonitrile are added to the boiling solution. The reaction mixture is boiled for 4 hours and is evaporated to dryness. Water is added to the residue. Thus 0.6 g. of 1-cyano-3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are obtained. Mp.: 236°C (from alcohol).

Analysis: $C_{14}H_{14}N_4O_2$

	Calculated:	Found:
C:	62.21%	61.61%
H:	5.22%	5.30%
N:	20.73%	20.41%

Example 16.

15 ml. of water and 0.7 g. of benzoyl chloride are added to 1 g. of 3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline and the pH value of the reaction mixture is held under stirring and cooling at a value of 10—11 hy adding a 10% solution of sodium hydroxide to the mixture. 1.3 g. of 3-benzoyl-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are obtained. Mp.: 258°C (from alcohol).

Analysis: $C_{20}H_{19}N_3O_3$

	Calculated:	Found:
C:	68.75%	68.60%
H:	5.48%	5.74%
N:	12.03%	12.05%

Example 17.

0.7 g. of benzoyl chloride are reacted with 1 g. of 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline according to the method described in Example 15 and thus 1 g. of 2-benzoyl-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo-[5,1-a]isoquinoline are obtained. Mp.: 185°C (from alcohol).

Analysis: $C_{20}H_{19}N_3O_3$

	Calculated:	Found:
C:	68.75%	68.52%
H:	5.48%	5.65%
N:	12.03%	11.83%

Example 18.

10 ml. of 2-N-hydrochloric acid solution are added to 0.5 g. of 2-acetylamino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline and the reaction mixture is boiled under reflux for half an hour. On cooling 0.5 g. of 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline-hydrochloride-dihydrate are crystallized, the product is identical to the product of Example 5. Mp.: 128—130°C.

Example 19.

15 ml. of 5% sodium hydroxide solution are added to 1.3 g. of 3-acetylamino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline and the reaction mixture is boiled for an hour under reflux. On cooling 0.8 g. of 3-amino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline are crystallized, the product is identical to the product of Example 1. Mp.: 234—236°C.

Example 20.

10 ml. of xylene are added to 1.0 g. of 3-(6,7-dimethoxy-3,4-dihydro-2H-1-isoquinolylidene)-methyl-5-propyl-1,2,4-oxadiazole and the reaction mixture is boiled for 8 hours under reflux. The solvent is evaporated *in vacuo* and the residue is recrystallized from aqueous alcohol. 0.7 g. of 2-butyryl-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline-hemihydrate are obtained. Mp.: 125—127°C.

14. 1 - Cyano - 3 - amino - 5,6 - dihydro - 8,9 - dimethoxy-imidazo[5,1 - a]isoquinoline and acid addition salts thereof.

15. 3 - Benzoylamino - 5,6 - dihydro - 8,9 - dimethoxy - imidazo[5,1 - a]isoquinoline and acid addition salts thereof.

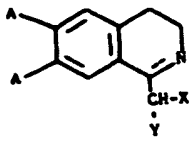
16. 2 - Benzoylamino - 5,6 - dihydro - 8,9 - dimethoxy - pyrazolo[5,1 - a]isoquinoline and acid addition salts thereof.

17. 2 - Butyrylamino - 5,6 - dihydro - 8,9 - dimethoxy - pyrazolo[5,1 - a]isoquinoline and acid addition salts thereof.

18. 2-Ethylamino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]isoquinoline and acid addition salts thereof.

19. Compounds according to claim 1 substantially as hereinbefore described.

20. A process for the preparation of 3-amino-imidazo[5,1-a]isoquinoline derivatives according to claim 1 wherein
A is as defined in claim 1,
D is hydrogen, and
Y is as defined in claim 1,
which comprises reacting a compound of the general formula II



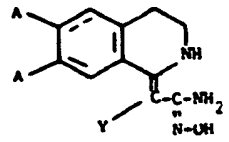
(II)

or an acid addition salt thereof,
wherein A and Y are as defined above, and X represents halogen with an alkali metal salt or an alkaline earth metal salt of cyanamide.

21. A process according to claim 20 wherein said alkali metal salt of cyanamide is sodium hydrogen cyanamide.

22. A process according to claim 20 or 21 wherein Y is cyano, phenyl or substituted phenyl.

23. A process for the preparation of the 3-amino-imidazo[5,1-a]isoquinoline derivatives according to claim 1 wherein
A is as defined in claim 1,
D represents hydrogen or acyl,
Y represents hydrogen, alkyl, or aralkyl or phenyl each optionally substituted by one or more substituents selected from halogen atoms, alkoxy and nitro groups,
which comprises acylating an isoquinolyl-acetamidoxime of the general formula



(III)

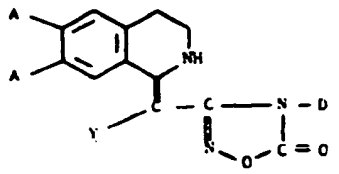
wherein A and Y are as defined above and allowing the O-acyl intermediate thus produced to be transformed to an imidazo [5,1-a] isoquinoline derivative under basic conditions.

24. A process according to claim 23 wherein acylation is performed with a sulphonyl chloride, carboxylic acid chloride or carboxylic acid anhydride in a basic medium.

25. A process according to claim 24 wherein acylation is performed in pyridine.

26. A process according to claim 23, 24 or 25 for the preparation of compounds of the general formula I wherein D represents an acyl group, which comprises acylating a corresponding compound of the general formula III wherein D is hydrogen with excess acylating agent.

27. A process for the preparation of pyrazolo[5,1-a]isoquinoline derivatives according to claim 1 wherein A is as defined in claim 1, Y is hydrogen, cyano, carbamoyl, alkyl, or aralkyl or phenyl each optionally substituted as defined in claim 1, and D is hydrogen,
which comprises subjecting compounds of the general formula



(IV)

(wherein A, Y and D are as defined above), to heating in a solvent or in a melt or to aqueous alkaline hydrolysis.

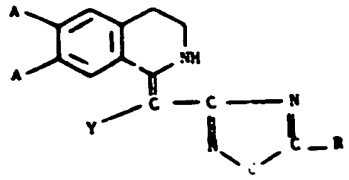
28. A process according to claim 27 wherein said solvent is xylene or tetralin.

29. A process according to claim 27 wherein the reaction is performed at a temperature above 100°C.

30. A process according to claim 27 wherein the reaction is performed by boiling with aqueous alkali metal hydroxide.

31. A modification of the process according to claim 27 for the preparation of pyrazolo-[5,1-a]isoquinoline derivatives according to claim 1 wherein A is as defined in claim 1, Y is as defined in claim 27 and D represents alkyl, aralkyl or cycloalkyl which comprises subjecting a corresponding compound of the general formula IV to alkaline hydrolysis.

32. A process for the preparation of pyrazolo[5,1-a]isoquinoline derivatives which comprises converting compounds of the general formula



(V)

(wherein A is as defined in claim 1, Y is hydrogen, alkyl, or aralkyl or phenyl, each optionally substituted as defined in claim 1 and R is alkyl, aryl or aralkyl each optionally substituted with halogen, nitro or alkoxy) under mildly alkaline conditions, or by heating in a solvent or in a melt to compounds of the general formula I (wherein D is an acyl group).

33. A modification of the process according to claim 32 which comprises subjecting said compound of the general formula V to strong alkaline hydrolysis to obtain a compound of the general formula I wherein D is hydrogen.

34. A process for the preparation of compounds according to claim 1 (wherein A is as defined in claim 1, Y is hydrogen, cyano, carbamoyl, alkyl or aralkyl or phenyl each optionally substituted by one or more substituents selected from halogen atoms, alkoxy and nitro D is alkyl, aralkyl or cycloalkyl) which comprises subjecting a corresponding compound of general formula I wherein D is hydrogen to reductive alkylation with an aldehyde or ketone.

35. A process for the preparation of imidazo[5,1-a]isoquinolidine derivatives according to claim 1 (wherein A is as defined in claim 1, Y is as defined as in claim 1 and D is alkyl, aralkyl or cycloalkyl) which comprises heating a corresponding compound of the general formula IV at a temperature above 100°C in a solvent or in melt form.

36. A process for the preparation of a compound according to claim 1 wherein A and D are as defined in claim 1 and Y is carbamoyl or alkoxycarbonyl, which comprises subjecting a corresponding compound wherein Y is cyano to hydrolysis or alcoholysis.

37. A process for the preparation of a compound according to claim 1 wherein A and Y are as defined in claim 1 and D is hydrogen, which comprises subjecting a corresponding compound whercin D is acyl to hydrolysis.

38. A process according to any of claims 20—37 including the step of reacting the compound of the general formula I so obtained with a mineral or organic acid, or setting free the base of the general formula I from an acid addition salt thereof.

39. A process according to any of claims 20—38, substantially as hereinbefore described with reference to any one of the Examples.

40. A pharmaceutical composition containing as active ingredient a compound of the general formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

41. A pharmaceutical composition according to claim 40 comprising at least one compound according to any of claims 2—18 as active ingredient.

42. A pharmaceutical composition according to claim 40 comprising 2-amino-5,6-dihydro-8,9-dimethoxy-pyrazolo[5,1-a]is quinoline or a pharmaceutically acceptable acid additi n salt thereof.

43. A pharmaceutical c mposition according to claim 40 comprising 3-benzylamino-5,6-dihydro-8,9-dimethoxy-imidazo[5,1-a]isoquinoline or a pharmaceutically acceptable acid addition salt thereof.

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